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Pharmacological treatment of Tourette syndrome

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ABSTRACT

Tourette syndrome (TS) is a highly heritable yet heterogeneous childhood onset disorder. The cardinal movement disorder required for diagnosis is tics. As persons with tics or TS often have obsessive/compulsiveness, inattention, hyperactivity, impulsivity, anxiety, and anger outbursts, the presence of tics should prompt clinicians to look for these other conditions. While randomized controlled trials provide valid evidence of efficacy for symptoms in isolation, implications for treatment of complex patients meeting criteria for multiple diagnoses is not always clear. In this review, the authors critically review factors influencing decisions whether and how to treat medically tics as well as OCD and ADHD in the presence of tics.

1. Introduction

Tics, the cardinal symptom of Tourette syndrome (TS), are patterned involuntary, "unvoluntary" (compelled by inner urge), or habitual movements (motor tics) or sounds (phonic tics), often preceded by a premonitory sensation (Dooley, Gordon, Wood, Camfield, & Camfield, 2003; Jankovic, 2001; Kurlan, 2010; Kompoliti & Goetz, 1998). The premonitory phenomenon helps in differentiation of tics from other jerk-like movements such as myoclonus and chorea, which occur without preceding urges (Kwak, Dat Vuong, & Jankovic, 2003; Woods, Piacentini, Himle, & Chang, 2005). Tics are quite common in otherwise normally developing children (Snider, Seligman, & Ketchen, 2002) and are approximately twice as common in children receiving special education services as those who are mainstreamed (Kurlan, 1994; Kurlan, Como, & Miller, 2002; Kurlan, Whitmore, Irvine, McDermott, & Como, 1994; Palumbo, Maughan, & Kurlan, 1997).

Although generally considered childhood disorders, tics can persist into adulthood, but usually with lower frequency and reduced intensity (Bloch & Leckman, 2009; Bloch, Peterson, & Scahill, 2006; Leckman, Zhang, & Vitale, 1998; Pappert, Goetz, Louis, Blasucci, & Leurgans, 2003). Adult onset tics usually represent re-emergence of childhood onset tics, but other causes of tics besides TS, such as drugs (e.g. CNS stimulants, cocaine, neuroleptics), Huntington disease, neuroacanthocytosis, autism, and other neurological disorders should be considered as possible etiologies. Most clinical trials and studies address treatment of tics in childhood, but some, particularly studies of new medications or other treatments, include or focus on adults (Chae, Nahas, & Wassermann, 2004; Gilbert, Budman, Singer, Kurlan, & Chipkin, 2014; Jankovic, Jimenez-Shahed, & Brown, 2010; Okun, Foote, & Wu, 2013; Scahill, Leckman, Schultz, Katsovich, & Peterson, 2003; Wilhelm, Peterson, & Piacentini, 2012).

Achieving the most effective treatment of tics in TS is contingent on proper diagnosis of the movement disorder and judicious use of available interventions. In many cases, no medication is needed and simple reassurance will suffice. When medication is prescribed, the goal is to reduce the tic frequency and intensity so that the tics no longer impair the patient's function at home, school, or at work, and no longer interfere with social activities and interactions. Achieving the most effective and safest treatment of the child or adult with TS requires thorough assessment and treatment for other cognitive and emotional problems (Carter et al., 2000; Gilbert, 2006; Singer, 2005; Zinner, 2004). Effective pharmacologic treatment is aided by collaborative, realistic assessment with the individual and family of tic-related and comorbidity-related impairment.

Treatment of tics in TS has been the subject of a number of excellent review articles (Jankovic & Kurlan, 2011a; McNaught & Mink, 2011; Wu, Harris, & Gilbert, 2010). These reviews include guidelines for medication selection, dosing, and monitoring for side effects. In this paper we will focus our review on oral pharmacological treatment for tic, ADHD, and OCD symptoms in TS but also discuss more broadly the issues influencing treatment decisions. In addition to oral medications, many patients with TS manifested chiefly by focal tics, such as blinking and cervical tics, may be treated with local injections of botulinum toxin (Kwak, Hanna, & Jankovic, 2000; Marras, Andrews, Sime, & Lang, 2001). This approach is particularly effective in the treatment of repetitive head jerking (so called

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"whiplash" tics), that can cause secondary myelopathy, and other potentially disabling tics (Dobbs & Berger, 2003; Krauss & Jankovic, 1996; Lin, Wang, Wong, Wu, & Lin, 2007; Muroi et al., 2002). Some tics are so severe and even life-threatening (hence the term "malignant TS") (Cheung, Shahed, & Jankovic, 2007) that they cannot be managed medically and in such cases deep brain stimulation may be considered (Mink, Walkup, & Frey, 2006). This therapeutic intervention is beyond the scope of this review and is covered elsewhere in this volume.

2. Treatment of the non-tic symptom spectrum in TS

2.1. Who should treat TS and its comorbidities?

An important treatment issue in TS is where to seek treatment if the primary care physician and/or patient desire specialty care. Often in persons with TS, cognitive, behavioral and emotional problems cause far more impairment than tics (Bernard, Stebbins, & Siegel, 2009; Carter et al., 2000). In both community and clinic settings, the majority of children and adults with tics or TS also have troublesome non-tic problems including symptoms of Attention Deficit Hyperactivity Disorder (ADHD), Obsessive Compulsive Disorder (OCD), other forms of anxiety, substance abuse, aggression, or anger control difficulties (Comings, 1994; Freeman, 2007; Kurlan et al., 2002; Zinner, 2004). Genetic studies also clearly demonstrate high rates of these same problems in families of TS probands, including both parents ("bilineal transmission") and even in family members who do not have tics (Comings & Comings, 1990; Grados & Mathews, 2008). Children diagnosed with autistic spectrum disorders often present with tics and may meet criteria for TS (Canitano & Vivanti, 2007; Comings & Comings, 1991; Lawson-Yuen, Saldivar, Sommer, & Picker, 2008). Thus whether we consider ADHD or OCD "comorbidities" of TS or manifestations within the spectrum of a heterogeneous neurobehavioral disorder, physicians involved in the management of patients with TS must be skilled in not only treating tics but the entire spectrum of symptoms that commonly affect patients with TS.

The roles of neurologists and psychiatrists have traditionally lead to fractionated care, particularly when the mental health diagnoses receive different (less) reimbursement by health insurance companies which prioritize medical (neurological) over mental health coverage. However, there are a number of other disorders in which neurological and psychiatric symptoms commonly co-exist. In addition to TS, other examples of such overlap include the adult and childhood epilepsies (Brodie, Chadwick, & Anhut, 2002; Franks, 2003; Hesdorffer et al., 2004), multiple sclerosis (Patten, Fridhandler, Beck, & Metz, 2003; Patten & Metz, 1997), cerebrovascular diseases (O'Brien, Erkinjuntti, & Reisberg, 2003; Robinson, 2003; Taragano, Allegri, Vicario, Bagnatti, & Lyketsos, 2001), Parkinson's disease (Klaassen et al., 1995; Mindham, Marsden, & Parkes, 1976), tardive dyskinesia (Klaassen et al., 1995), and Huntington's disease (Bonelli, Wenning, & Kapfhammer, 2004). Thus in these and many other neurological conditions, neurologists should be skilled in managing the associated behavioral or psychiatric problems. Given the high prevalence of movement disorders in psychiatric patients, it is similarly reasonable for psychiatrists to feel some level of comfort with diagnosis and evaluation of movement disorders. In many cases, the best approach is for these disciplines to work collaboratively with multiple specialties to provide the most comprehensive and expert care.

With these considerations in mind, clinicians who see large numbers of TS patients should be prepared to treat non-tic symptoms of TS. A reasonable expectation might be that neurologists providing or directing fairly comprehensive care for TS would treat ADHD and OCD in many cases, but refer to psychiatrists those TS patients manifesting severe OCD, psychosis, auditory hallucinations, mania, and suicidal ideation. Similarly, psychiatrists treating TS would treat tics in many cases, but might refer to neurologists patients demonstrating particularly severe tics, suspected seizures, drug induced movement disorders, suspected secondary tic disorders, or progressive cognitive impairment.

2.2. Evidence-based treatment of ADHD in persons with TS

Most double blind, randomized, placebo-controlled clinical trials of treatments for behavioral diagnoses attempt to recruit a relatively pure sample of individuals whose impairing symptoms emanate from the primary diagnosis. Thus, subjects who suffer from other DSM-V diagnoses are typically excluded, particularly if these other diagnoses are severe enough to require current treatment. In the cases of conditions like TS, where meeting criteria for two or more DSM-V diagnoses is the rule rather than the exception, this practice favors validity at the expense of generalizability (Gilbert & Buncher, 2005). As most studies have been small, and the majority of large, rigorous clinical trials of ADHD and OCD treatment exclude TS, it is difficult to know whether estimates of effect size in clinical trials are generalizable to TS in the community. Furthermore, while the practice of evidence-based medicine is encouraged, it is important to acknowledge that most patients with TS referred to a specialty clinic would be excluded from the controlled trials that provide "the evidence".

Treatment of ADHD in TS is more complicated than treatment of ADHD without co-occurring TS, for at least two main reasons. First, in some individuals with TS, tics or other repetitive behaviors may worsen when stimulant medications are prescribed for ADHD. That is, even when inattention, hyperactivity, and impulse control problems reliably and reproducibly diminish on stimulants, tics, compulsions, or stereotypies can concurrently escalate, often in a dose-sensitive (Bloch, Panza, Landeros-Weisenberger, & Leckman, 2009) fashion. While observed by clinicians for many years, this stimulant-induced exacerbation is not a universal occurrence and indeed may be quite uncommon (Denckla, Bemporad, & MacKay, 1976; Tourette Syndrome Study Group, 2002). In such cases, a more beneficial outcome may be achieved with nonstimulants for ADHD, such as atomoxetine, or combining a stimulant with an alpha 2 adrenergic agonist or a dopamine receptor blocking agent or tetrabenazine. Indeed, when patients present with the combination of troublesome tics and ADHD we often treat the tics first and add a stimulant later. This strategy should be carefully explained to the patients and their parents, particularly those who (often incorrectly) perceive this risk of stimulants outweighing their potential benefits. A second important challenge in TS is the potential for diagnostic misclassification of both inattention and hyperactivity symptoms of ADHD. In TS with anxiety, OCD, or high functioning autism, sometimes what appears by observation or standardized DSM-V based ratings (Conners, Sitarenios, Parker, & Epstein, 1998; DuPaul, Power, Anastopoulos, & Reid, 1998; Wolraich et al., 2003) to be a *deficit in attention* is actually wholly or in part a *misdirection of attention* ("attention direction disorder"). The individual with TS, instead of paying attention to what is salient to the rest of the classroom or family, may attend to internal premonitory tic urges, poorly filtered sensations, obsessions, ruminations, or areas of special interest. In such cases, treatment with a stimulant may increase the child's internally directed focus. The result can be increased tics, increased OCD symptoms, increased autistic behavior or stereotypies, marked agitation, or what parents sometimes describe as a "zombie" phenomenon where empathy is further diminished and/or the child's spontaneity and creativity are stultified. Clinical experience suggests that many such children

are better off not taking stimulants or they may benefit from treatments directed against their OCD, anxiety, or other symptoms that may interfere with their "attentiveness". Similarly, care should be taken to distinguish tics and stereotypies, which are coordinated, repetitive and patterned movements, from the general hyperkinesis and fidgeting characteristic of ADHD-hyperactivity. Although some complex tics may appear stereotypic, recurrent or persistent stereotypies are more common in patients with autistic spectrum disorder or some other neurobehavioral disorder other than TS. In rare cases, hyperkinesis may be chorea, myoclonus, or some drug-induced movement disorder. Suspicion of these movement disorders should generate a referral to a movement disorder neurologist.

Interpreting clinical trial data also poses challenges. To achieve an accurate estimate of TS effects on results of ADHD treatment would require at a minimum, large, rigorous clinical trials in ADHD which included a substantial number of individuals with TS. Deriving an estimate by comparing results across separate non-TS and TS studies would be confounded by other differences in inclusion criteria, treatment practices, and the inherent inaccuracies in clinically assessing OCD and ADHD severity using subjective rating scales. Moreover, a broadly representative TS sample would not be recruited into placebo-controlled mono-therapy studies because patients required pharmacologic treatment of ADHD and OCD would be automatically excluded (Gilbert & Buncher, 2005).

The best estimates we have of treatment outcomes for childhood ADHD comes from the multimodal treatment of ADHD (MTA) study, which compared, in 579, 7–9 year old children, four regimens: (1) very intensive behavioral interventions provided by experts, (2) stimulant medications prescribed by experts, (3) the combination of these interventions, and (4) routine community care. The MTA study showed that core ADHD symptoms were effectively reduced by stimulants in most children and that these benefits persisted during active expert treatment over 14 months (Multimodal Treatment of ADHD Cooperative Group, 1999). Unfortunately, outcomes of all 4 groups converged over 3–8 years, with persistent high rates of hospitalization for mental illness, substance abuse, and incarceration or involvement of the justice system (Molina, Flory, & Hinshaw, 2007; Molina, Hinshaw, & Swanson, 2009). No comparable, controlled, long-term studies are available in TS. However, it is unlikely that a TS plus ADHD cohort would have fared better than the children in the MTA study. Thus, a take-home message for clinicians treating children with TS plus ADHD is that there is a relatively high long-term risk of adverse social outcomes. Nevertheless, most patients with the combination of TS and ADHD achieve high quality of life when properly managed by knowledgeable physicians.

With regard to short term benefits of ADHD treatment, there are a number of randomized, placebo-controlled trials of ADHD treatment in children with tics or TS using stimulants (Castellanos, Giedd, & Elia, 1997; Gadow, Nolan, Sverd, Sprafkin, & Schneider, 2008; Tourette Syndrome Study Group, 2002) and a selective norepinephrine reuptake inhibitor (Allen, Kurlan, & Gilbert, 2005). Effects of these, along with ADHD treatments with guanfacine, clonidine, deprenyl, and desipramine were combined in a meta-analyses of nine double-blind, randomized, placebo controlled studies of ADHD treatment in TS (Bloch et al., 2009). A main aim of these studies was to see if ADHD could be effectively treated without making tics worse. Taken together, the results of these studies show that stimulants, alpha-2 adrenergic agonists, and norepinephrine reuptake inhibitors are more effective than placebo in reducing ADHD symptoms in children with TS. In addition, in the two largest studies, for most participants on active treatment with methylphenidate, clonidine, or atomoxetine, tics improved (Allen et al., 2006; Tourette Syndrome Study Group, 2002). Thus, stimulants as well as other pharmacologic treatments are quite effective in the treatment of ADHD and are usually not contraindicated in the presence of TS. In patients with ADHD who also have co-existent troublesome tics it is considered prudent practice to treat the tics first (see below) before initiating anti-ADHD therapies.

2.3. Evidence-based treatment of OCD in persons with TS

Estimating OCD treatment outcomes in TS involves the same obstacles discussed above for ADHD. However, treatment of OCD in the presence of tics has been even less systematically investigated. Based on a small post-hoc analysis, it appears that both cognitive behavioral therapy and selective serotonin reuptake inhibitors (SSRIs) are less effective in OCD with tics than in OCD with no tics (Garcia, Sapyta, & Moore, 2010; The Pediatric OCD Treatment Study (POTS) Team, 2004).

The best estimates we have of treatment outcomes for childhood OCD comes from the pediatric obsessive compulsive disorder treatment study (POTS), which compared, in 112 children, 7–17 year old, four regimens: (1) very intensive cognitive behavioral therapy (CBT) provided by experts, (2) selective serotonin reuptake inhibitor medication prescribed by experts, (3) the combination of these interventions, and (4) placebo (The Pediatric OCD Treatment Study (POTS) Team, 2004). The POTS study showed that active treatments reduced OCD symptoms at 12 weeks. However, a more clinically useful take home message from the study is the proportion of individuals in each group who achieved an excellent outcome: 3% in the placebo group; 21% in the sertraline group; 39% in the CBT group, and 54% in the combined treatment group. Although these short-term outcomes seem disappointing, individualized approach using different combinations of behavioral and pharmacologic therapies, often provides satisfactory relief of symptoms (Scahill, Erenberg, & Berlin, 2006). The current expert consensus is that the pharmacological treatment of choice for OCD with TS is the same as for OCD without TS: SSRIs, or clomipramine. A better outcome however may be achieved with concurrent cognitive behavioral therapy.

3. Treatment of the tic symptom spectrum in TS

3.1. When to treat tics?

The first decision point for treatment interventions for movement disorders is to recognize the phenomenology of the dominant movement disorder. Phenomenology is the basis for the selection of the most appropriate therapeutic option. Thus tics generally respond to different treatments than other hyperkinetic movement disorders such as dystonia or myoclonus, or psychogenic movement disorders that may resemble tics. The next step is to decide whether the movement disorder is troublesome enough to require treatment at all. It is important to recognize that there are no preventive or disease modifying therapies for any of the movement disorders. However, currently available symptomatic treatments, when properly selected and applied, can provide at least partial benefits. The indications for consideration of medical treatment should be the presence of (1) social impairment (including classroom or workplace disruption due to phonic tics), (2) functional impairment, (3) pain, or (4) neurological or other deficit as a result of the tics (or self-injurious behavior) (Cheung et al., 2007). Even when none of these four criteria are met, individuals or families may still request treatment if tics are annoying. Conversely, even when one or more of these criteria are met, some individuals or parents will chose not to treat due to their perceptions that the potential benefits do not outweigh the possible risks. This scenario poses significant difficulties for both

patients and care-providers as the parents' perceptions may be irrational and not in the best interest of the child. An emerging area of research involves understanding more systematically the reported differences between parent and children in tic and non-tic related impairment in TS (Cavanna, Luoni, & Selvini, 2013; Termine, Luoni, & Selvini, 2014). In addition to pharmacologic therapies consideration should be given to non-medical (e.g. behavioral or surgical) treatment options (Piacentini, Woods, & Scahill, 2010; Piacentini et al., 2010).

3.2. Three tiers of evidence-based pharmacological treatment tics

Once a decision to try medication for tics has been reached, there are essentially three tiers of oral medications (Jankovic & Kurlan, 2011b). The first-tier medications are alpha 2 adrenergic agonists guanfacine (Scahill, Chappell, & Kim, 2001) and clonidine (Du, Li, & Vance, 2008; Leckman et al., 1991; Tourette Syndrome Study Group, 2002). These agents are relatively well tolerated except for sedation, lightheadedness, and dry mouth as the most common side effects. Both can improve ADHD symptoms, but the authors use them more frequently for the treatment of impulse control disorder (Palumbo et al., 2008; Sallee, Lyne, Wigal, McGough, 2009; Sallee et al., 2009; Tourette Syndrome Study Group, 2002). Clonidine may be more helpful for sleep initiation at night, but daytime sedation limits its use (Tourette Syndrome Study Group, 2002). Both can also be readily combined with psychostimulants (Tourette Syndrome Study Group, 2002). It is reasonable in many cases for primary care physicians to initiate treatment with guanfacine or clonidine, subsequently referring cases which are refractory.

The second tier oral, tic-suppressing medications includes a plethora of medications which appear, usually in small or open label studies, to have modest benefit. Some of these have been used off-label for decades (Robertson, 2000). Effects of these medications tend to be modest, but some may be chosen in order to concurrently treat tics plus another symptom. Sometimes the motivation for using these medications is to avoid the third tier, the dopamine receptor blocking agents, whose risks are more intimidating for individuals and families. Topiramate, an antic-onvulsant, has been found in one double-blind, placebo-controlled trial to effectively reduce tics (Jankovic et al., 2010). Although not all patients can tolerate this drug and some develop cognitive and other adverse effects, it can be helpful particularly if patients would also benefit from migraine prophylaxis (Lewis, Winner, & Saper, 2009). Results for the anticonvulsant levetiracetam have been mixed (Awaad, Michon, & Minarik, 2005; Hedderick, Morris, & Singer, 2009; Smith-Hicks, Bridges, Paynter, & Singer, 2007). The use of dopamine agonists pergolide (no longer marketed) (Gilbert et al., 2003) and ropinirole (Anca, Giladi, & Korczyn, 2004) for tics initially appeared promising, but a controlled trial of pramipexole, another dopamine agonist, showed no benefit (Kurlan et al., 2012).

The third tier medications include the anti-dopaminergic drugs, either dopamine receptor blocking agents, also known as neuroleptics or antipsychotics, or dopamine depletors, such as tetrabenazine. Only two medications are currently approved by the United States Food and Drug Administration for tic suppression in TS: haloperidol and pimozide. In addition to these two agents, a number of other dopamine receptor blocking agents have been used successfully to treat tics. There are, however, only a few head-to-head comparisons of these agents. In general, the typical agents pimozide, haloperidol, and fluphenazine, and the high potency atypical agent risperidone appear comparable (Bruggeman et al., 2001; Gilbert, Batterson, & Sethuraman, 2004; Rose & Moldofsky, 1977; Sallee, Nesbitt, Jackson, Sine, & Sethuraman, 1997; Singer, Gammon, & Quaskey, 1985; Wijemanne, Wu, & Jankovic, 2013). However, there are a large number of potential neurologic, cognitive, emotional, metabolic, and cardiac side effects of this class of medications which limit their use (Kompoliti, Goetz, Morrissey, & Leurgans, 2006). Of particular concern is the risk of tardive movement disorders (Correll & Kane, 2007; Klaassen et al., 1995; Silva, Muñoz, Daniel, Barickman, & Friedhoff, 1996; Wonodi, Reeves, & Carmichael, 2007). Fortunately, this risk appears to be quite low in children with TS, but the risk is greater in adult patients. Competent monitoring for emergence of drug-induced movement disorders is critical.

The practice parameter for treatment of tics in TS published in 2006 by the Medical Advisory Board of the Tourette Syndrome Association www.tsa-usa.org (Scahill et al., 2006) still provides useful information on effect sizes for symptom suppression for dopamine receptor blocking agents and other medications. Based on trial design, the Advisory Board categorized medications into three groups: A – those with short term safety and efficacy demonstrated in at least two randomized placebo-controlled trials; B – those with short term safety and efficacy demonstrated in at least one placebo-controlled study; C – those supported by clinical experience and open label studies. Levels of evidence from the 2006 practice parameter, dose ranges, and monthly costs are shown in Table 1. A meta-analysis estimating beneficial effects of pimozide was also published (Pringsheim & Marras, 2009). More recently, a few small clinical trials have demonstrated benefit in TS from aripiprazole (Budman, Coffey, & Shechter, 2008; Seo, Sung, Sea, & Bai, 2008; Yoo, Joung, & Lee, 2013) and metoclopramide (Nicolson, Craven-Thuss, Smith, McKinlay, & Castellanos, 2005). These drugs, similar to other neuroleptics, however, can cause a variety of tardive syndromes (Kenney, Hunter, Davidson, & Metoclopramide, 2008; Pena, Yaltho, & Jankovic, 2010, 2011), although this still appears to be extremely rare in TS.

Although dopamine-receptor blocking drugs are among the most effective anti-tic medications, because of concern about weight gain and potential tardive complications, other drugs are increasingly used in the treatment of tics, despite lack of rigorous clinical trials. In patients with significantly impairing tics, tetra-benazine may also be considered. This is based both on the mechanism of action, as well as on results of open label studies performed over many years (Jankovic, 2009; Kenney, Hunter, Mejia, & Jankovic, 2007; Paleacu et al., 2004; Sweet, Bruun, Shapiro, & Shapiro, 1974). This dopamine-depleting drug has the advantage over the dopamine receptor blocking agents in that it does not cause tardive dyskinesia or weight gain, but it still can be associated with some adverse effects, such as sedation, slowness of movement, depression, akathisia and insomnia (Kenney et al., 2007; Ondo, Jong, & Davis, 2008).

Clinical practice supports judicious use of medications when tics cause impairment. Sequential monotherapy and starting with a low dose at bedtime and titrating up slowly diminishes sedation and other side effects. The aim is to find the lowest tolerable dose that satisfactorily reduces tics. Table 2 shows common medications and methods for titrating up on the dose. Discontinuing medications after an adequate trial, or when symptoms seem to have spontaneously remitted, should be done gradually, not abruptly. Medications doses may also be reduced during less stressful periods, e.g. summer vacations.

Costs may also influence decisions, particularly when families have no health insurance or expensive co-pays (see Table 1). Thus in the absence of head-to-head comparisons, one may choose medications like topiramate and tetrabenazine for patients who are overweight and avoid medications like risperidone and other neuroleptics.

3.3. How do we know which medications work best for tics?

Evaluating tic outcomes in clinical trials and in clinical practice is not straightforward (Gilbert & Buncher, 2005; Jeon, Walkup, &

Table 1
Levels of evidence and dose ranges from the Tourette Syndrome Association Medical Advisory Board Practice Guideline, see text.

Oral medication name generic (BRAND)	Evidence Level	Dose minimum (mg)	Dose maximum (mg)	Minimum Dose cost of generic per month (30 day supply)	Maximum dose cost of generic per month	Minimum dose cost of brand name per month	Maximum dose cost of brand name per month
Aripiprazole (ABILIFY)	NA	5	30			547.0	765.0
Baclofen (LIORESAL)	C	10	20	8.0	69.0		
Clonazepam (KLONOPIN)	NA	0.5	2	10.0	14.0	80.0	133.0
Clonidine (CATAPRES)	B	0.10	0.30	4.0	7.5	40.0	71.5
Fluphenazine (PROLIXIN)	B	1	10	11.0	27.0		
Guanfacine (INTUNIV)	B	1	2 (generic)	10.0	25.0	266.34*	266.34
Haloperidol (HALDOL)	A	0.50	10	6.0	22.0		
Levetiracetam (KEPPRA)	NA	250	750	21.36*	27.04*	95.0	142.0
Metoclopramide (REGLAN)	NA	5	10	7.0	2.5	31.0	48.0
Olanzapine (ZYPREXA)	C	2.5	20	138.10*	901.96*	327.0	1286.0
Ondansetron (ZOFRAN)	NA	4	8 (generic)	306.0	1020.0	750.0	1287.0
Pimozide (ORAP)	A	1	2			57.80	75.12*
Risperidone (RISPERDAL)	A	0.25	4	19.61*	37.49*	161.0	473.0
Tetrabenazine (XENAZINE)	C	12.5	25			1825.47*	3638.53*
Topiramate (TOPAMAX)	NA	25	200	13.83*	26.13*	72.0	220.0
Ziprasidone (GEODON)	B	20	80			273.0	332.5

NA indicates the agent was not included in the guideline. Costs are retail, in U.S. dollars, from DrugPriceInfo.com as of January, 2014, except those with *calculated using rxpricequotes.com (zip code=45209; radius=100miles; average=all pharmacies – prices often vary). Tetrabenazine may also be available in the U.S. through applying to a patient assistance program.

Woods, 2013). Tics wax and wane over minutes, hours, days, and lifetime (Leckman et al., 1998; Peterson & Leckman, 1998; Peterson, Pine, Cohen, & Brook, 2001), and individuals may choose to enroll in a study or begin medication in practice during a time when tics are at a maximum. Subsequent improvement may then be medication-induced or may represent spontaneous remission as part of the natural course of the disease rather than due to treatment. As nearly all published trials in TS are short-term studies, it is quite possible that long-term treatment benefits are overestimated. In one long-term, open-label study involving 268 patients with TS, fluphenazine at an optimal dose of 3.24 ± 2.3 mg/day (range 0.5–12 mg/day), continued to provide benefit for an average of 2.6 ± 3.2 years (range 0.01–16.8 years) (Sallee et al., 1997). Commonest side effects included drowsiness, fatigue or both, observed in 70 (26.1%) of patients, but there were no cases of tardive dyskinesia.

As is the case for other movement disorders, rating scales are used in clinical trials and often in practice. The rating scale most often used for tics in TS is the Yale Global Tic Severity Score (YGTSS) (Leckman, Riddle, & Hardin, 1989). In clinical trials, the primary treatment outcomes may be either the total YGTSS, which includes a subjective 0–50 point metric of tic impairment, or the 0–50 point total tic scale only, which is less subjective but does not capture global life-impairment effects. The YGTSS tic-only scores capture the phenomenology, with 5 points each for number, frequency, intensity, complexity, interference, and separate scores for motor vs. phonic tics.

It is important to note that the YGTSS is only a rough metric of symptom severity and does not necessarily reflect an individual's perceptions or a clinician's ratings of symptoms. For example, an individual with both mild motor and mild phonic tics and not interested in treatment could have a higher score than a person with a current single very severe and impairing motor tic. Another difficulty is that the 5 equally scored components are not likely to be equally responsive to treatment or equally valued by patients. For example, it may be more important to an individual to reduce the frequency or severity of tics than to reduce the number or complexity of them. A two point reduction in either frequency or severity might be highly valued clinically despite the small effects statistically. A meta-analysis modeling improvement in behavioral treatment trials estimated that a 25% reduction in the YGTSS tic score corresponds to a positive response in the clinical global impression scale. However, meaningful global improvement may also occur in ways not captured by the YGTSS tic score (Jeon et al., 2013).

Given the prevalence of non-tic symptoms, perhaps a TS composite score might be considered. Such a score might be helpful if more basic, upstream neurobiological mechanisms in TS are identified through research and targeted by novel treatments that simultaneously reduce multiple symptoms. Such a scale would be difficult to develop and interpret and would have little added value over current practice in clinical trials, where symptom domains are rated on separate rating scales. Thus in interpreting the results of a study for patient care, it is prudent to look at not only at the primary outcome but secondary effects seen in other rating scales. Global measures of function and improvement can also aid in interpreting the usefulness of an agent in a clinical trial. A significant global benefit in a placebo controlled trial may be important, even if the tic score does not register much change.

As has been reviewed elsewhere (Cubo, Gonzalez, & Singer, 2013; Gilbert, 2006; Gilbert & Buncher, 2005), a few additional caveats are in order related to study design. Uncontrolled, open label studies often overestimate benefit because many non-drug factors may influence the outcome. However, they may also be able to recruit more severely affected patients and may allow treatment of co-occurring symptoms. Also, long-term observational trials more closely approximate the “real-life” situation

Table 2
Titration of medications for tic suppression.

Alpha 2 adrenergic agonists – tier 1	
Clonidine 0.1 mg tabs or in patch form	0.05 mg (½ tab) at bedtime for 3 days, then increase every 3–7 days by 0.05 mg to target dose of 0.05 to 0.1 mg 3 times per day
Guanfacine 1 mg tabs	0.5 mg po (1/2 tab) at bedtime for 3 days, then increase every 3–7 days by 0.5 mg to target dose of 0.5–2 mg 2 times per day
Other agents – tier 2	
Topiramate	25 mg at bedtime for 1 week, then increase weekly by 25 mg to target dose of 50 to 75 mg two times per day
Baclofen	10 mg at bedtime for 3 days, then increase every 3–7 days by 10 mg to target dose of 10 to 30 mg two to three times per day
Benzodiazepines	Various agents (clonazepam, diazepam) are sometimes used for severe exacerbations (status ticcus) or for chronic treatment of tics with anxiety
Ropinirole	Several studies suggest modest benefit of low doses of dopamine agonists, conceptually similar to treating restless legs syndrome
Botulinum toxin	Injections for focal or dystonic tics
Antipsychotics – tier 3	
Fluphenazine, Haloperidol, Pimozide, Risperidone	1 mg at bedtime for one week. Increase as needed every 3–7 days to target dose of 1 to 4 mg daily. Can divide dose.
Ziprasidone	20 mg at bedtime for 1 week. Increase as needed weekly by 20 mg to target dose of 20 to 100 mg per day. Can divide dose.
Aripiprazole	2 mg at bedtime for 1 week. Increase as needed weekly by 2–5 mg to target dose of 2 to 30 mg daily. Can divide dose.
Tetrabenazine	12.5 mg at bedtime for 1 week. Increase as needed weekly by 12.5–25 mg to target dose of 25 to 150 mg daily. Can divide dose.

when patients with multiple symptoms are often treated with multiple medications. Placebo-controlled studies, while desirable to generate evidence-based data and valid assessments of treatment effects, have their own limitations in that they are usually short, inflexible, and the results may not be generalizable as the enrollment is available only to those who meet strict inclusion–exclusion criteria. A recent study of placebo controlled trials in TS estimated a tendency toward improvement on placebo which approached statistical significance but had a small effect size (Cohen's $d=0.16$) (Cubo et al., 2013). Furthermore, both patient concerns about placebo and requirements for monotherapy may reduce willingness of severely affected individuals to participate, particularly if the agent being studied is already marketed and can be more easily obtained through routine clinical care. Therefore, the results of clinical trials, whether placebo controlled, active comparator, or open label may have value but should be applied cautiously to the general population of TS patients.

There are many other emerging or experimental treatment approaches that may be eventually incorporated into the therapeutic armamentarium in TS. These include: (1) Cannabinoids, such as delta9-tetrahydrocannabinol (Curtis, Clarke, & Rickards, 2009); (2) AZD5213 (novel histamine H3 receptor inverse agonist) (Jucaite, Takano, & Bostrom, 2012); (3) Ecopipam (a D1 antagonist) (Gilbert et al., 2014); (4) SD-809 ER (a deuterated form of tetrabenazine) (Jimenez-Shahed & Jankovic, 2013); (5) forms of repetitive transcranial magnetic stimulation (Kwon, Lim, & Lim, 2011; Wu, Maloney, & Gilbert, 2014); (6) novel surgical approaches (Viswanathan, Jimenez-Shahed, Baizabal Carvallo, & Jankovic, 2012); and other novel therapeutic interventions (Termine, Selvini, Rossi, & Balottin, 2013).

4. Summary

TS is a complex disorder with many symptoms which may benefit from education, behavioral training, medical treatment, and sometimes more invasive treatments. Treatment requires a thoughtful approach to the full spectrum of problems, focusing on impairment. Education and collaboration with the individual and family is essential. Current medical treatments have suboptimal effectiveness, and clinical trial literature, while useful, should be interpreted thoughtfully. Advocacy groups like the Tourette Syndrome Association offer many useful resources to patients, families, schools, and treating professionals which may also mitigate the impairment from TS symptoms.

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